

REMARKS

Claims 1-11, 15, 17 and 18 are pending and under active consideration in the instant application. Claim 7 has been cancelled without prejudice. Applicants reserve the right to pursue cancelled subject matter in one or more related applications. Claim 17 has been amended to delete dependency from a withdrawn claim. Claims 3, 5, 6, 8, 9 and 18 have been amended to clarify the subject matter of the present claims.

Support for the claim amendments can be found in the specification. Support for the amendment to claim 2 can be found, *inter alia*, at paragraphs [0030], [0037], and [0046]. Support for the amendment to claim 3 can be found, *inter alia*, at paragraphs [0024], [0037], and [0377]. Support for the amendment to claim 5 can be found, *inter alia*, at paragraphs [0038] and [0377]. Support for the amendment to claim 6 can be found, *inter alia*, at paragraph [0058]. Support for the amendment to claims 8 and 9 can be found, *inter alia*, at paragraphs [0039] and [0377]. Support for the amendment to claim 18, can be found, *inter alia*, at paragraphs [0377] and [0378] of the specification. No new matter has been added.

Applicants request that the amendments and remarks made herein be entered and made of record in the file of the above-identified application. Following entry of the amendments made herein, claims 1-6, 8-11, 15, 17, and 18 will be pending and under active consideration in the instant application.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

The Examiner has rejected claims 3, 5-11 and 18 under 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claim the invention.

In particular, the Examiner has rejected claim 3 as allegedly indefinite for reciting that the claimed composition has a “50% fiber slurry” wherein the amount of the polymer in the slurry is not stated. Applicants respectfully disagree. The use of the term “slurry” in the instant application is in full accord with its commonly understood meaning, *e.g.*, “a watery mixture of insoluble matter” as set forth in Exhibit A, Webster’s Ninth New Collegiate Dictionary (1987). One of skill in the art can readily determine an appropriate amount of fiber that when mixed with liquid will generate a slurry. Moreover, the specification provides examples of amounts of fiber that may be mixed with distilled water or a NaCl solution to form the slurry (*see, e.g.*, paragraphs [0127] and [0377] of the specification). The composition of claim 3 thus comprises 50% of poly- β -1 \rightarrow 4-N-acetylglucosamine polymer

fiber slurry, that is 50% of a mixture of poly- β -1 \rightarrow 4-N-acetylglucosamine polymer fiber and liquid that is in the form of a slurry. Accordingly, Applicants submit that, as interpreted in light of the specification by one of skill in the art, the phrase is not indefinite.

The Examiner has rejected claim 5 as allegedly indefinite for inclusion of the phrase “at least 0.125% CaCl_2 solution,” wherein the method of calculation of the percentage is not defined. Applicants respectfully disagree. Applicants submit that because the claim recites the percentage of a solution in the composition, one of skill in the art would interpret said percentage to be calculated on a volume/volume basis in accordance with common scientific practice of mixing two liquids on a volume/volume basis. Thus, one of skill in the art can readily determine the metes and bounds of the percentage recitation in claim 5 and, accordingly, this claim is not indefinite.

The Examiner has also rejected 6-9 and 18 for inclusion of a percentage term, wherein the method of calculation of the percentage is not defined.

Applicants respectfully disagree. First, Applicants note that claim 7 has been cancelled without prejudice, rendering the rejection moot. To avoid any potential ambiguity with respect to claims 8 and 9, Applicants have amended the claims to recite a 0.9% NaCl solution. Applicants submit that one of skill in the art would have interpreted the phrase “1.0 ml of a 0.9% NaCl” to refer to a NaCl solution; thus, the amendment does not narrow the scope of the claims.

Turning to the rejection at hand, claims 6 and 18 recite “10% CaCl_2 ” and claims 8 and 9 recite “0.9% NaCl.” Applicants submit that because each of claims 6, 8, 9 and 18 recites a percentage of a salt in a solution, one of skill in the art would interpret said percentage to be calculated on a weight/volume basis in accordance with common scientific practice of mixing salt and liquid on a weight/volume basis. Thus, one of skill in the art can readily determine the metes and bounds of the percentages in claims 6, 8, 9 and 18 and, accordingly, these claims are not indefinite.

The Examiner has rejected claim 18 for inclusion of the phrase, “in the presence of a 10% calcium chloride solution,” arguing that it is doubtful that the final composition of the gel comprises 10g of calcium chloride per 100 ml of gel. Applicants respectfully disagree. The method of claim 18 requires only that a sufficient amount of a 10% calcium chloride solution be present during the mixing of isolated platelets and poly- β -1 \rightarrow 4-N-

acetylglucosamine polymer fiber slurry to produce a platelet-poly- β -1 \rightarrow 4-N-acetylglucosamine polymer fiber gel; it does not require that the final composition comprise 10% calcium chloride. Applicants have amended claim 18 in order to clarify that the calcium chloride be “in an amount effective to elicit formation of a platelet-poly- β -1 \rightarrow 4-N-acetylglucosamine polymer fiber gel.” This requirement was implicit in claim 18 as originally filed; thus, the amendment does not narrow the scope of the claims.

The recitation that the calcium chloride be in an amount effective to elicit formation of a platelet-poly- β -1 \rightarrow 4-N-acetylglucosamine polymer fiber gel does not render claim 18 indefinite. Using the specification for guidance, for example, following the teachings of paragraph [0378] one of skill in the art can readily determine an amount of 10% calcium chloride solution that is appropriately used in the method of gel formation of claim 18. Moreover, the specification exemplifies a suitable amount of 10% calcium chloride in the present methods, such as 0.125 ml of 10% calcium chloride per 5 ml of each of PRP and poly- β -1 \rightarrow 4-N-acetylglucosamine polymer fiber slurry (*see, e.g.*, paragraph [0377]). Thus, one of skill in the art can readily determine the metes and bounds of claim 18 and, accordingly, claim 18 is not indefinite.

In view of the foregoing, Applicants submit that the rejection of claims 3, 5-6, 8-11 and 18 under 35 U.S.C. § 112 is in error and should be withdrawn.

THE PRESENT INVENTION

The present invention, as embodied in independent claims 1, 8, 9 and 18, is drawn to compositions comprising poly- β -1 \rightarrow 4-N-acetylglucosamine polymer and platelets, as well as to methods of their manufacture and/or use. The methods of the claimed invention permit the storage of platelets which would otherwise be destroyed, and result in compositions that have many therapeutic applications.

Claims 1, 8 and 9 are directed to various aspects of the compositions of the invention, and claim 18 is directed to a method of making a composition of the invention which is in the form of a gel. In claim 1, the poly- β -1 \rightarrow 4-N-acetylglucosamine polymer is purified; in claims 8 and 9, the poly- β -1 \rightarrow 4-N-acetylglucosamine polymer is in the form of fiber, and in claim 18 the poly- β -1 \rightarrow 4-N-acetylglucosamine polymer is in the form of a polymer fiber solution.

THE REJECTION UNDER 35 U.S.C. § 102(a) SHOULD BE WITHDRAWN

The Examiner has rejected claims 1-11 and 18 under 35 U.S.C. § 102(a) as anticipated by Okamoto *et al.*, 2002, Science 5:643-649 (“Okamoto”) in light of Veech, U.S. Patent No. 4,663,289 (“Veech”) and Male *et al.*, U.S. Patent No. 5,292,524 (“Male”). Applicants submit that the rejection under Okamoto is in error for the reasons set forth below.

A claim is anticipated under 35 U.S.C. § 102 only if each and every element and limitation as set forth in the claim is found, either expressly described or inherently present, in a single prior art reference. *Glaxo, Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1995). There must be *no differences* between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.* 927 F.2d. 1565, 1576 (Fed. Cir. 1991).

Okamoto discloses the use of chitin and chitosan as a means of activating or aggregating freshly-obtained platelets. However, Okamoto does not disclose a composition comprising poly- β -1 \rightarrow 4-N-acetylglucosamine polymer in any shape or form, and for at least this reason does not anticipate claims 1, 8, or 9. Nor does Okamoto disclose a method of making a gel comprising platelets and poly- β -1 \rightarrow 4-N-acetylglucosamine polymer, and for at least this reason does not anticipate claim 18.

By way of explanation, poly- β -1 \rightarrow 4-N-acetylglucosamine polymer is a different material from chitin and chitosan. In particular, as made clear in the specification, chitin and chitosan as used in the art ambiguously refer to a family of compounds which differ widely in terms of physical and chemical properties, exhibiting varying molecular weights, varying degrees of acetylation and species-specific contaminants (*see* specification, *e.g.*, at paragraph [0003]). It is also clear from the claims that poly- β -1 \rightarrow 4-N-acetylglucosamine polymer is distinct from chitin and chitosan: for example, independent claim 18 requires that platelets bind to the pGlcNAc polymer fibers in greater numbers relative to the amount of platelets that would bind an equivalent amount of chitosan fibers. Thus, Okamoto’s teaching of the use of chitin or chitosan to activate or activate freshly-obtained platelets is not a teaching of a method of making a gel comprising poly- β -1 \rightarrow 4-N-acetylglucosamine polymer and platelets, as claimed in independent claim 18, nor is it teaching of a composition comprising poly- β -1 \rightarrow 4-N-acetylglucosamine polymer and platelets, as claimed in independent claims 1, 8 and 9. Accordingly, Okamoto does not anticipate any of the independent claims.

Okamoto does not anticipate claims 1, 8 and 9 for at least one additional reason. The embodiment of the invention as claimed in independent claims 1, 8 and 9 relate to the use of preserved platelets. Okamoto does not anticipate independent claims 1, 8 and 9 because the reference does not disclose the use of preserved platelets. In Okamoto, PRP or washed platelets for use in the studies were isolated from fresh whole blood. Okamoto does not discuss any storage of the PRP or platelets between isolation and use. Thus, Okamoto does not disclose the use of preserved platelets as required by independent claims 1, 8 and 9.

Moreover, the embodiment of the invention as claimed in dependent claim 10 is directed to a pharmaceutical composition. In Okamoto, all studies were conducted *ex vivo* in test tubes. Okamoto's studies of mixing chitin or chitosan with platelets or platelet-rich plasma were performed experimentally *in vitro*, yielding compositions that are not necessarily suitable for pharmaceutical use, and Okamoto does not expressly disclose a composition that is a pharmaceutical composition. Thus, Okamoto does not anticipate a pharmaceutical composition as claimed claim 10.

Okamoto also does not anticipate claims 6 and 18 for at least one additional reason. The embodiment of the invention as claimed in independent claim 18 relate to a method for producing a platelet-poly- β -1 \rightarrow 4-N-acetylglucosamine polymer fiber gel, and employs calcium chloride solution in an amount effective to elicit formation of such a gel. The Examiner cites U.S. Patent No. 4,663,289 to Veech ("Veech") and U.S. Patent No. 5,292,524 to Male ("Male") in support of her position that Okamoto anticipates the present claims. Veech relates to cell culture/preservation media and Male relates to the use of platelets as therapeutic agents. As noted by the Examiner, Veech and Male respectively describe the calcium content of blood plasma and modified Tyrode's Buffer used in Okamoto. In particular, Tables I and II of Veech state that plasma has 1.06 mM free calcium ions, and Male states that modified Tyrode's buffer has 0.14g/l of calcium chloride, *i.e.*, approximately 0.014% calcium chloride. Thus, Okamoto never mixes a population of isolated platelets with poly- β -1 \rightarrow 4-N-acetylglucosamine polymer fiber slurry in the presence of a 10% calcium chloride solution, as recited in claim 18. Thus, while there may have been calcium present in the composition produced in the studies of Okamoto, there is nothing to suggest that the calcium was present in an amount effective to elicit formation of a gel. Thus, the calcium present in Okamoto's method does not inherently anticipate the use of the amount of calcium recited in claim 18. Similarly, because Okamoto does not describe a composition comprising

0.125% of a 10% calcium chloride solution, the calcium present in the composition produced by Okamoto's studies cannot anticipate the composition of claim 6.

For at least the foregoing reasons, Okamoto does not teach each and every element of claims 1,6, 8, 9, 10 and 18. Accordingly, Okamoto cannot anticipate the claims. Because Okamoto does not anticipate any of independent claims 1, 8, 9, and 18, the reference also does not any claim dependent from these claims.

Applicants therefore respectfully submit that the rejection of claims 1-11 and 18 as anticipated by Okamoto in light of Veech and Male is in error and should be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

The Examiner has rejected claims 1-11, 15, 17 and 18 under 35 U.S.C. § 103(a) as unpatentable over Okamoto or U.S. Patent No. 5,614,204 to Cochrum ("Cochrum") in combination with U.S. Patent No. 5,858,350 to Vournakis *et al.*, ("Vournakis") in light of Veech and Male. Applicants respectfully disagree with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998). Further, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981 (CCPA 1974).

The Rejection over Okamoto and Vournakis in view of Veech and Male

In Okamoto, the effect of chitin or chitosan particle suspensions on platelet compositions was determined (*see* Okamoto Abstract and Experimental section, page 643, lines 2-3). Contact of platelets with the chitin or chitosan suspensions was found to induce both aggregation and activation of platelets.

Okamoto shows that chitin and chitosan elicit activation or aggregation of platelets. In Okamoto, a composition comprising chitin or chitosan and platelets is a byproduct of the study. Nowhere does Okamoto provide a teaching or suggestion for the use of such a composition. At most, Okamoto hints at the use of chitin or chitosan as a coagulation or activation agent in itself. Thus, Okamoto does not provide any motivation for making a composition comprising chitin or chitosan and platelets, much less the motivation for combining poly- β -1 \rightarrow 4-N-acetylglucosamine polymer and platelets for therapeutic or platelet preservation applications. Thus, Okamoto does render obvious the presently claimed invention.

Vournakis does not remedy the deficiencies of Okamoto. Vournakis is directed to the use of poly- β -1 \rightarrow 4-N-acetylglucosamine as a hemostatic device. Thus, Vournakis teaches the application of a poly- β -1 \rightarrow 4-N-acetylglucosamine to a patient, to stop bleeding, but does not suggest any or provide any motivation for making a composition of poly- β -1 \rightarrow 4-N-acetylglucosamine with platelets.

Neither Veech nor Male remedy the deficiencies of Okamoto alone or in combination with Vournakis. Veech relates to cell culture/preservation media and Male relates to the use of platelets as therapeutic agents. Neither teaches nor relates to the use or manufacture of a composition of poly- β -1 \rightarrow 4-N-acetylglucosamine with platelets.

Applicants therefore respectfully submit that the rejection of claims 1-11, 15, 17 and 18 over Okamoto in combination with Vournakis in view of Veech and Male is in error and should be withdrawn.

The Rejection over Cochrum and Vournakis in view of Veech and Male

In Cochrum, biopolymers, including chitosan, are combined with PRP and the combination administered intravenously in the proximity of bleeding, a rupture, a fistula, etc. to form an occlusive clot. As discussed *supra*, Vournakis, while teaching the benefits of over chitin and chitosan, does not teach or suggest a composition comprising pGlcNAc and platelets, much less suggest that such a composition.

The Examiner's obviousness rejection is predicated on the notion that one of skill in the art would look beyond the teachings of Cochrum and identify poly- β -1 \rightarrow 4-N-acetylglucosamine as a substitute for the biopolymers disclosed therein. The Court of Customs and Patent Appeals addressed a similar situation in *In re Herschler*, 591

F.2d 693, 200 U.S.P.Q. 711 (CCPA 1979), when it held that the Board had wrongly rejected the appealed claims as obvious. In *Herschler*, the applicant taught the use of DMSO to enhance transdermal penetration of a number of compounds, and claimed the process of applying to the skin a mixture comprising DMSO and a physiologically active steroid. 591 F.2d at 695, 200 U.S.P.Q. at 712. The Board rejected the claims as obvious over a primary reference (the Lubowe patent), which disclosed a hair lotion containing an estrogenic hormone and a solubilizing agent other than DMSO, combined with a secondary reference (Faust), which taught that DMSO is a safe and effective solubilizing agent for cosmetic or dermatologic use. The CCPA reversed the Board's rejection on the grounds that disclosure of the primary reference was already complete for its intended purpose, so that one of ordinary skill in the art would not have been motivated to use the DMSO of the secondary reference.

The Federal Circuit also addressed this issue in *Winner v. Wang*, 202 F.3d 1340, 1349, 53 U.S.P.Q.2d 1580, 1586 (Fed. Cir. 2000) when it held that there was no motivation to combine the primary reference (Johnson) with the secondary reference (Moore) because there was "no apparent disadvantage" to the device taught by Johnson. *See Winner*, 202 F3d at 1349, 53 U.S.P.Q.2d at 1587.

Applying the standard of the *Herschler* and *Winner* case law discussed above, it is improper to combine the teachings of Cochrum with Vournakis. Accordingly, the rejection of the instant claims over Cochrum over Vournakis is in error.

Neither Veech nor Male remedy the deficiencies of Cochrum alone or in combination with Vournakis. As discussed *supra*, neither teaches nor relates to use or manufacture of chitin, chitosan or pGlcNAc polymers or to the use or manufacture of preserved platelets.

For the foregoing reasons, Applicants submit that the rejection of claims 1-11, 15, 17 and 18 over Okamoto or Cochrum in combination with Vournakis in view of Veech and Male is in error and should be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks into the file of the above-identified application. Applicants believe that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

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